REMARKS

I. Status of the Claims. By this Amendment, claims 8-22 are pending. Claims 9, 11, 13-15 and 17 have been withdrawn from consideration by the Examiner as being drawn to a non-elected invention.

Applicants note that the claim status summary found in the Office Action at page 2, first paragraph appears unrelated to the subject application. The status of the claims referred to in the remainder of the Office Action, however, is consistent with the summary given in the previous paragraph.

Claims 10, 12, and 16 have been amended, without prejudice or disclaimer, to be directed to a polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency hybridization conditions to an isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO. 3. Support for the amended claims is found throughout the specification, e.g., at page 10, lines 6-7, page 11, lines 20-29, page 15, line 23 through page 16, line 10, page 21, lines 18-20. Accordingly, no new matter has been added to the application by the amendments to claims 10, 12, and 16.

Withdrawn claim 9 has been amended to delete the word "polypeptide" from the expression "Drosophila Recombination Associated Protein (DRAP) polypeptide." The scope of claim 9 is unchanged. Accordingly, the amendment to claim 9 does not add new matter to the application.

Claims 12, 13 (withdrawn), 14 (withdrawn), 15 (withdrawn), and 16 have been amended to clarify that the defined segment of DNA recited in each respective claim is not co-injected with oligonucleotide, but rather is present within a cell. Support for the amended claims

is found in the specification at page 21, lines 18-30, page 22, lines 3-8, and Examples 7 and 8. Accordingly, no new matter has been added to the application by these amendments to claims 12-16.

New claims 20-22 recite subject matter that was formerly present respectively in original claims 10, 12, and 16. Accordingly, claims 20-22 do not add new matter to the application.

II. Unity of Invention. The Examiner has made the lack of unity of invention "final." The Examiner's position is that the finding of a lack of unity of invention is proper because the technical feature of DRAP is taught by Eisen et al. (PNAS, 85:7481-7485, 1988) ("Eisen et al."). The Examiner's position is not well taken. As discussed below at length in the sections addressing rejections under 35 U.S.C. §§ 102 and 103, Applicants' position is that DRAP is patentable over the disclosure of Eisen et al. and all other prior art of record and can therefore serve as the required special technical feature. Accordingly, withdrawn claims are 9, 11, 13-15 and 17 have not been cancelled. Applicants respectfully reserve the right to request rejoinder of the withdrawn claims upon the determination of allowable subject matter in the examined claims.

III. Co-pending Application. Applicants enclosed a Notification of Co-pending Application, bringing the Examiner's attention to Applicants' co-pending application, serial no. 10/353,174, filed January 28, 2003. The co-pending application is cited on an accompanying Information Disclosure Statement. A copy of the published application is also enclosed.

IV. Drawings. Formal drawings are enclosed herewith.

V. Claim Objections. The term "DRAP" no longer appears in claims 10, 12, or 16. The objections are therefore believed to be moot.

VI. Claim Rejections. The rejections set forth by the Examiner are summarized and addressed as follows:

(i) Rejections Under 35 U.S.C. § 101. Claim 10 is rejected as being drawn to non-statutory subject matter. In response, without conceding the correctness of the rejection, claim 10 has been amended to be directed to "isolated" polypeptides. An "isolated" polypeptide is defined in the specification at page 8, lines 28-30, as "one that is unaccompanied by at least some of the material with which it associated in its natural state." Hence an "isolated" polypeptide is not a naturally occurring product-- it is "made by man." *Diamond v Chakrabarty,* 447 US 303, 206 USPQ 193 (1980). The amendment to claim 10 is believed to address and overcome the rejection of claim 10 as being directed to non-statutory subject matter. Reconsideration of claim 10 and withdrawal of the rejection thereof under 35 U.S.C. § 101 is requested, accordingly.

(ii) Rejections Under 35 U.S.C. § 112.

(a) Under 35 U.S.C. § 112, second paragraph. Claims 10, 12, and 16 have been rejected as indefinite for recitation of the expression "DRAP polypeptide." In response, without conceding the correctness of the rejection, claims 10, 12, and 16 have been amended. The expression "DRAP polypeptide" no longer appears in thes claims. The rejection is thus believed to have been addressed and overcome. Reconsideration of claims 10, 12, and 16 and withdrawal of all rejections thereof under 35 U.S.C. § 112, second paragraph is requested, accordingly.

(b) Under 35 U.S.C. § 112, first paragraph. Claims 10, 12, and 16 have also been rejected as allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventors had possession of the claimed invention at the time the application was filed ("written description"). In response, without conceding the correctness of the rejection, claims 10, 12 and 16 have been amended. These claims are now directed to an isolated polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency hybridization conditions to an isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO. 3.

Amended claims 10, 12, and 16 comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The claims are highly analogous to the "product by function" example discussed in the USPTO's training guidelines on the written description requirement. (See Example 14, "Product by Function," at page 53 of USPTO guidelines available at http://www.uspto.gov/web/menu/written.pdf.) According to the guidelines, a claim directed to a genus of proteins having the properties having high (95%) identity and the same enzymatic activity as a single disclosed protein species complies with the written description requirement. In the instant claims, the recitation of "high stringency hybridization conditions" substitutes for a particular level of sequence identity.

Claims 10, 12, and 16 comply with the written description requirement for at least the following reasons. Proteins encoded by nucleic acids that hybridize under high stringency conditions to a nucleic acid selected from the group consisting of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO. 3 are variants of a Drosophila Associated Protein (DRAP) of SEQ ID NO: 4. The specification contemplates such DRAP variants (see specification, e.g., at page 11 line 29, et seq. (DRAP-encoding sequences modified by transitions transversions, deletions, insertions, etc.) and page 15, line 23 et seq. (Nucleic acids encoding wild-type or variant DRAP polypeptides may be introduced into cells; purified DRAP polypeptides that are function-conservative variants

of SEQ ID NO: 4). The disclosed DRAP of SEQ ID NO: 4 is representative of the genus covered by the claims because all members thereof have the features of being encoded by a nucleic acid that hybridizes to DRAP-encoding sequences under high stringency hybridization conditions and exhibiting recombinase and topoisomerase activities. These features ensure a high degree of sequence identity among all members of the genus. As set forth in the aforementioned written description Guidelines, "one of ordinary skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus." *Id.* at page 56.

For the reasons set forth above, Applicants submit that claims 10, 12, and 16 comply with the written description requirement set forth in 35 U.S.C. § 112, first paragraph.

Claims 10, 12, and 16 have also been rejected under for allegedly failing to comply with the "enablement" requirement of 35 U.S.C. § 112, first paragraph. The Examiner alleges the specification does not reasonably provide enablement for any function-conservative variant of a DRAP polypeptide of SEQ ID NO: 4. Applicants submit that the specification enables one of ordinary skill in the art to make and use the full scope of the invention claimed in amended claims 10, 12, and 16 without undue experimentation.

As discussed above, the amended claims are now directed to an isolated polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency hybridization conditions to a DRAP-encoding nucleic acid. One of ordinary skill in the art would expect that a protein that is encoded by a nucleic acid that hybridizes to a DRAP-encoding nucleic acid under high stringency hybridization conditions and exhibits two biochemical activities exhibited by DRAP would be a functional homolog of DRAP. In particular, one of ordinary skill in then art would expect that any of the polypeptides

recited in claims 12 and 16 could be used in the same methods in which a DRAP of SEQ ID NO: 4 can be used. Hence, one of ordinary skill in the art would expect that the polypeptides recited in claims 12 and 16 could be used in the respective methods of homologous recombination recited therein without undue experimentation. Accordingly, the specification teaches how to use the full scope of the invention claimed in claims 12 and 16.

The specification also contains sufficient information to allow one of ordinary skill in the art "to make" the full scope of the invention of claims 10, 12, and 16. When routine procedures can be used to identify those DRAP variants that have the characteristics recited in the claims, making and screening even large numbers of variants is not undue experimentation. *Hybritech, Inc. v Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert denied,* 480 US 947 (1987). Applicants submit it is well accepted that at the time the application was filed it was routine in the art to make either random or directed variants in any cloned gene. The specification sets forth specific methods for expressing DRAP-variants, purifying them if necessary (e.g., by affinity chromatograph), measuring topoisomerase and recombinase activities, and determining whether nucleic acids hybridize under high stringency hybridization conditions. Thus, using techniques set forth in the specification and other techniques well known in the art, one of ordinary skill in the art could readily screen large numbers of DRAP-variants for those that retained topoisomerase and recombinase activities, without undue experimentation. Given the routine nature of making and screening the DRAP-variants, 35 U.S.C. § 112, first paragraph does not require that Applicants be able to predict ahead of time which DRAP variants fall within the scope of the claims.

For all of the reasons set forth above, Applicants submit the specification complies with all of the requirements of 35 U.S.C. §112, first paragraph. Reconsideration of

claims 10, 12, and 16 and withdrawal of all rejections thereof under 35 U.S.C. §112, first paragraph is requested, accordingly.

(iii) Rejections Under 35 U.S.C. § 102(b). Claims 8 and 10 are rejected as allegedly anticipated by Eisen et al. (Proc. Natl. Acad. Sci USA, 85:7481-7485, 1988) ("Eisen et al."). Claims 18 and 19 are rejected as allegedly anticipated by or, in the alternative, obvious over Eisen et al. The rejections are respectfully traversed.

Claims 8, 18 and 19 are not anticipated because, contrary to the Examiner's position, Eisen et al. does not describe an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v Union Oil Co. of California*, 814 F.2d 628, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "To serve as an anticipation reference when the reference is silent about the inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (emphasis added). Inherency requires that the prior art "necessarily functions in accordance with, or includes, the claimed limitations." *MEHL/Biophile Int'l Corp. v Milgraum,* 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305 (Fed. Cir. 1985) (emphasis added). It is not sufficient that there is a "probability" that one of ordinary skill in the art following the prior art would arrive at the claimed invention. *Id.*

The Examiner's position is that Eisen et al. "teach the purification of a recombinase from *Drosophila melanogaster* embryos." The Examiner concludes that Eisen et al.

thus anticipates claims drawn to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4. The Examiner's position is not well taken. Eisen et al. fails to disclose the sequence of any polypeptide. Hence, Eisen et al. does not expressly describe the limitation of an amino acid sequence of SEQ ID NO: 4. Nor does Eisen et al. inherently describe a polypeptide comprising the amino acid sequence of SEQ ID NO: 4. Eisen et al. merely describes a recombinase activity from *Drosophila melanogaster* embryos. There is no evidence, however, that the recombinase activity is due to a polypeptide comprising an amino acid sequence of SEQ ID NO: 4. One of ordinary skill in the art would understand that *Drosophila melanogaster* embryos would likely contain more than one enzyme exhibiting recombinase activity. The recombinase activity described in Eisen et al. therefore does not necessarily indicate the presence of a protein comprising the amino acid sequence of SEQ ID NO: 4. The limitation of "an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4" is therefore not inherently disclosed in Eisen et al.[1]

Claims 8, 18 and 19 each include the limitation of "an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4." For the reasons set forth above, Eisen et al. does not set forth such a limitation, either expressly or inherently. Eisen et al. therefore does not anticipate claim 8, 18, or 19.

[1] Applicants also note that the enzymatic properties of the a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 differ from the recombinase activity described in Eisen et al. in at least two important respects. The recombinase activity described in Eisen et al. did not require exogenous ATP, i.e., it was ATP-independent. The enzymatic activity of a protein comprising the amino acid sequence of SEQ ID NO: 4 requires ATP, i.e., it is ATP-dependent. Additionally, a protein comprising the amino acid sequence of SEQ ID NO: 4 exhibits both recombinase and topoisomerase activity. There is no evidence from the disclosure of Eisen et al. that the recombinase activity described therein is associated with a topoisomerase activity. These differences further support Applicants' position that the recombinase activity disclosed in Eisen et al. is not inherently due to a polypeptide comprising the amino acid sequence of SEQ ID NO: 4.

The rejection of claims 18 and 19 as, in the alternative, obvious over Eisen et al. is also predicated on the Examiner's position that Eisen et al. inherently discloses an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4. Because the underlying premise of the alternative obviousness rejection is not well founded, claims 18 and 19 are not obvious over Eisen et al.

With regard to claim 10, Applicants submit that, for the reasons already set forth above, Eisen et al. does not disclose expressly or inherently an isolated polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency conditions to an isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3. Eisen et al. therefore does not anticipate claim 10.

For all of the reasons set forth above, it is submitted that none of claims 8, 10, 18, or 19 is anticipated by or, in the alternative obvious over, Eisen et al. Applicants respectfully request reconsideration of claims 8, 10, 18, and 19 and withdrawal of all rejections thereof under 35 U.S.C. § 102(b) or, alternatively, under 35 U.S.C. § 103(a), accordingly.

(iv) Rejections Under 35 U.S.C. § 103(a). Claims 12 and 16 have been rejected as allegedly obvious over Eisen et al. and Zarling et al. (U.S. Patent No. 5,763,240). The rejections are respectfully traversed.

Applicants first traverse on grounds that claims 12 and 16 depend from a claim that is not obvious over the prior art of record and, therefore, they are also not obvious over the prior art of record. Hence, claims 12 and 16 have been amended to depend from claim 10. Accordingly, claims 12 and 16 are now directed respectively to methods for targeting mutagenesis and promoting gene disruptions of a defined segment of DNA by introducing an

isolated polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency conditions to an isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3 and an oligonucleotide homologous to the segment of DNA into a cell. As set forth above in the discussion of the rejections under section 102(b), claim 10 is not anticipated by Eisen et al. With respect to the obviousness rejection, nor is there any suggestion in Eisen et al. to modify the disclosure therein to arrive at an isolated polypeptide that exhibits recombinase and topoisomerase activities and is encoded by a nucleic acid that hybridizes under high stringency conditions to an isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3. Hence, claim 10 is not obvious over Eisen et al. Nor does Zarling et al. include any suggestion that would lead one of ordinary skill in the art to modify the disclosure of the cited prior art to arrive at the isolated polypeptide of claim 10. Zarling et al., therefore, does not cure the defect in Eisen et al. Accordingly, claim 10 is not obvious over Eisen et al. or Zarling et al., either separately or in combination. Because claims 12 and 16 depend from claim 10, neither are these claims obvious over the combination of Eisen et al. and Zarling et al.

Even if, arguendo, Eisen et al. did inherently disclose a polypeptide of SEQ ID NO: 4 (which Applicants do not believe it does), claims 12 and 16 would not be obvious over the combination of Eisen et al. and Zarling et al. To sustain an obviousness rejection, the prior art must include both a motivation to combine the references and an expectation of success for arriving at the claimed invention. In the instant case, there is no reasonable expectation that a protein with recombinase and topoisomerase activities could be derived from the disclosure of Eisen et al. First, the recombinase activity described in Eisen et al. is an ATP-independent

activity. The protein having the amino acid sequence of SEQ ID NO: 4 exhibits an APT-dependent activity. Hence, one of ordinary skill in the art would not expect the assay described in Eisen et al. could be used successfully to purify a polypeptide of SEQ ID NO: 4. Furthermore, the polypeptide of SEQ ID NO: 4 includes a topoisomerase activity that was not described in Eisen et al. In the recombinase assay described in Eisen et al. and also used in the instant specification, the topoisomerase activity leads to the production of linear molecules, and severely reduces the number of observed nicked circular molecules. (See Example 6, specification at page 34 et seq.) Hence, due to its topoisomerase activity, a purification based on recombinase activity would not be expected to yield a polypeptide of SEQ ID NO: 4, because the purified protein would not yield the expected nicked circular molecules. Finally, Applicants note that the polypeptide of SEQ ID NO: 4 ultimately was not purified using the recombinase assay described in Eisen et al., but was only purified after the gene encoding the protein was cloned and the protein was expressed in *E. coli*. Hence, the successful purification of DRAP required that the inventors depart significantly from the methods described in Eisen et al. and, more generally, required the inventors use non-standard, less predictable methods to obtain pure DRAP. In summary, the significant differences between the biochemical properties of the protein of SEQ ID NO: 4 and the biochemical properties of the recombinase described in Eisen et al. show that, contrary to the Examiner's position, there was not a reasonable expectation of success in purifying the recombinase activity described in Eisen et al. for use in the methods of claims 12 and 16. Accordingly, for this reason additionally the obviousness rejection of claims 12 and 16 should be withdrawn.

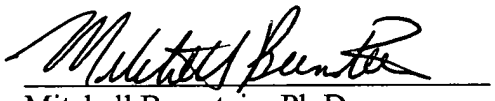
For all of the reasons set forth above, it is submitted that claims 12 and 16 are not obvious in view Eisen et al. and Zarling et al. Reconsideration of claims 12 and 16 and withdrawal of the rejections thereof under 35 U.S.C. § 103(a) is requested, accordingly.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Mitchell Bernstein, Ph.D.
Reg. No. 46,550
Agent for Applicant

DARBY & DARBY, P.C.
Post Office Box 5257
New York, NY 10150-5257
Phone (212) 527-7700